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## Featured Article

## Declining incidence of dementia: A national registry-based study over 20 years

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## Abstract

**Introduction:** The aim of this study was to investigate the registry-based national time trends in incidence and prevalence rates of dementia from 1996 to 2015.**Methods:** We assessed annual incidence and prevalence using longitudinal data from nationwide registries on dementia status and demographics on all residents  $\geq 65$  years old in Denmark.**Results:** Our population comprised 2 million people, of whom 152,761 were diagnosed with dementia. The age- and sex-adjusted incidence rate increased, on average, by 9% annually from 1996 to 2003, followed by a 2% annual decline, while total prevalence increased during the whole period.**Discussion:** This is the first study to report continuous time trends of incidence and prevalence in an entire national population. The incidence rate has declined steadily since 2003, while the total prevalence is still increasing. Future health care planning on prevention and treatment of dementia should take these findings into account.© 2019 The Authors. Published by Elsevier Inc. on behalf of the Alzheimer's Association. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

## Keywords:

Dementia; Incidence; Prevalence; Time trend; Epidemiology; Registry study; Nationwide study

## 1. Introduction

In 2015, the World Alzheimer Report estimated that 46.8 million people worldwide were living with dementia and projected an increase to 131.5 million by 2050 [1]. The magnitude and potential consequences of the expected increase in prevalence have led to a stronger focus on the potential for prevention and on finding a cure for Alzheimer's disease (AD) and other dementia disorders.

The risk of developing dementia is influenced by a combination of lifestyle and genetic factors. In a recent Lancet Commission article, Livingston et al. presented a model for

quantifying the impact of individual factors on overall risk of dementia [2]. The authors concluded that approximately 35% of the risk of developing dementia was potentially modifiable, encompassing mainly midlife and late-life risk factors such as hypertension, obesity, smoking, physical inactivity, diabetes, depression, social isolation, and hearing loss [2]. The Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability indicated that a multifaceted intervention program aimed at at-risk elderly people may prevent cognitive decline by focusing on cardiovascular risk factors [3]. In high-income countries, treatment of cardiovascular risk factors has improved and the focus on healthy lifestyles has increased during the last three decades [4]. Thus, it is plausible that, with general improvement in health and better control of risk factors, prevention of dementia may be possible to some extent.

Recent follow-up studies in large population-based cohorts indicated a possible decline in the incidence of dementia in the elderly during the past 10–42 years [5–11].

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Nevertheless, study results are inconsistent and, in some studies, the declining incidence was driven mainly by certain subgroups of either men, women, or specific subtypes of dementia [5,7,8].

Although population-based cohort studies offer detailed, systematic data on the individual participants, they have limitations, such as small cohorts, discontinuous data collection with long follow-up intervals, high dropout rates, recruitment from a small geographical area, and selection bias. Denmark's unique national registries enable linkage between a wide range of registries, including, for example, demographic and continuous health care data at an individual level for every resident [12]. Consequently, it is possible to explore time trends in an entire population based on high quality health care data from the secondary sector. Investigating time trends in incidence and prevalence of dementia is vital in planning future health care services and, hence, the ability to provide the best care and treatment for people with dementia.

The aim of this study was to investigate registry-based time trends in incidence and prevalence rates of dementia in an entire national population over a 20-year period. We hypothesized that the incidence of dementia may have declined in recent years, despite increasing prevalence.

## 2. Methods

We linked nationwide population data from the Danish Civil Registration System to information about dementia status using data from the Danish National Patient Registry, the Danish Psychiatric Central Research Register, and the Danish National Prescription Registry [12–15]. Every individual living permanently in Denmark is given a unique personal identification number, enabling linkage of data from Danish registries [13].

### 2.1. Registries and data

The Danish National Patient Registry and the Danish Psychiatric Central Research Register began registering data on all hospital admissions in 1977 and 1969, respectively, and in 1995, they began collecting data from emergency departments and hospital-based outpatient clinics [12,14]. At every patient contact, date of admission and discharge, and primary and optional secondary diagnosis have been registered according to the International Classification of Diseases, 8<sup>th</sup> revision (ICD-8) from 1977 to 1993 and the 10<sup>th</sup> revision (ICD-10) from 1994 [12,14]. ICD-9 was never implemented in Denmark [12]. The Danish National Patient Registry has collected information on filled prescription medication since 1995. Data include date of dispensing, dose, strength, and the Anatomical Therapeutic Chemical code (ATC code) [15]. Because of the implementation of ICD-10 and opening of the Danish Prescription Registry, the observation period was defined as January 1, 1996 to December 31, 2015.

### 2.2. Definition of dementia

A diagnosis of dementia was defined as either a registered dementia diagnosis in the Danish National Patient Registry or the Danish Psychiatric Central Research Register ([Supplementary Table S1](#) lists the diagnostic codes), or as having filled at least one prescription for an anti-dementia drug (ATC: N06D, see [Supplementary Table S2](#), which lists ATC codes for pharmaceutical treatment of dementia). Date of dementia onset was defined as the date of the first dementia diagnosis registered or the date of the first prescription filled, whichever came first.

### 2.3. Study population

People were included in the study upon turning 65 years, or if they were between 65 and 110 years old and registered as living in Denmark at some point from 1996 to 2015. Owing to the potential risk of misregistration, people older than 110 years were censored. The study population will be referred to as people aged 65 years and older.

#### 2.3.1. Incidence study

Incident cases were defined as people diagnosed with dementia, according to the abovementioned definition, for the first time within a given calendar year. People diagnosed with dementia before the age of 65 were excluded because we wanted to investigate incident cases in people aged 65 years and older. Individuals were censored when they were diagnosed with dementia, emigrated, were lost to follow-up, died, turned 110 years old, or at the end of the study period, whichever came first.

#### 2.3.2. Prevalence study

Prevalent cases were defined as people aged 65 years or older registered with a dementia diagnosis from 60 years of age, as a previous study showed that the validity of dementia diagnoses in the Danish registries given before the age of 60 years is low [16]. The rest of our study population served as the reference group. Individuals were censored when they emigrated, were lost to follow-up, died, turned 110 years old, or at the end of the study period, whichever came first.

### 2.4. Statistical analysis

Trends in incidence rates were tested with survival analysis techniques using Poisson regression analysis evaluating the calendar year as a time-dependent covariate. Incidence rates were calculated for men and women in strata of five-year age groups (65–69, 70–74, 75–79, 80–84, and 85+). Trends in prevalence were evaluated as annual period prevalence percent by comparing the number of person-years lived by people with dementia to the total number of person-years lived in the study population each year. Prevalence period percent was calculated for men and women in strata of five-year age groups (65–69, 70–74, 75–79, 80–84,

Table 1

Demographic data for all Danish residents aged 65 years and older; total number of people living with dementia; and the percentage of people living with dementia presented for the first and the last year in the 20-year observation period. The distribution is shown for men, women, age groups, median age, and interquartile range.

	1996			2015		
	All (n)	Dementia (n)	(%)	All (n)	Dementia (n)	(%)
All	803,334	14,019	1.75	1,055,984	36,129	3.42
Men	332,857	4554	1.37	481,331	13,271	2.76
Women	470,477	9465	2.01	574,653	22,858	3.98
Age (years)						
65-69	225,551	838	0.37	353,724	2036	0.58
70-74	208,162	1849	0.89	274,746	4185	1.52
75-79	163,644	2875	1.76	187,236	6492	3.47
80-84	116,090	3693	3.18	122,514	8607	7.03
85-89	63,162	3177	5.03	74,933	8744	11.67
90+	26,725	1587	5.94	42,831	6065	14.16
Median age	74.2	82.1		72.9	83.2	
IQR	69.5-80.2	76.6-86.8		68.8-79.3	77.5-88.2	

Abbreviation: IQR, Interquartile range.

85-89, and 90+). Prevalence period percent will be referred to as prevalence rates. Total incidence was evaluated as the total number of new dementia cases each year, while total prevalence was evaluated as point prevalence on January first.

Supplemental analyses of incidence by birth year were made to assess a possible birth cohort effect.

The analyses were performed using SAS, version 9.4 (SAS Institute Inc., Cary, NC). This study was approved by the Danish Data Protection Agency, Statistics Denmark, and the Danish Health and Medicines Authority.

### 3. Results

Between 1996 and 2015, there were 1,999,375 people (men: 920,093; women: 1,079,282) aged 65 years and older living in Denmark. A total of 152,761 people were diagnosed with dementia (men: 57,977; women: 94,784) observed over 16,944,630 person-years (men: 7,415,232; women: 9,529,398). During the 20-year study period, 170,478 people had been living with a dementia diagnosis (men: 64,559; women: 105,919).

The population for the prevalence study was followed over 17,541,315 person-years. Of these, 16,986,832 were lived without dementia (men: 7,439,899; women: 9,546,933) and 554,483 with dementia (men: 188,936; women: 365,547).

Table 1 shows the age and sex distribution of the total elderly population and of people with dementia in 1996 and 2015. As shown, the total elderly population increased from 803,334 in 1996 to 1,055,984 in 2015, while the median age decreased from 74.2 years in 1996 to 72.9 years in 2015. The percentage of people with dementia increased over the 20-year period for all age groups, and the trend was most pronounced in the oldest age groups.

Fig. 1A and B show time trends in incidence rates in women and men, respectively. Incidence rates were significantly higher in 2015 than in 1996 in all age groups in both men and women, except for men and women aged 65-69 years. The increase in incidence rates was most dominant in the oldest age groups. However, the increased incidence rates from 1996 to 2015 reflected a steep increase from 1996 to 2003, followed by stabilization/fluctuation until 2009 and 2010, and then a moderate decline from 2010 to 2015. This time trend was most predominantly observed in the oldest age groups. When assessing trends in the incidence rate adjusted for age and sex from 1996 to 2003 and from 2004 to 2015, we found an average annual increase in incidence rate of 9% from 1996 to 2003. From 2004 to 2015, the incidence rate decreased by 2%, on average, annually. The total incidence percentage of dementia increased from 0.58% in 1996 to 0.72% in 2015. The additional analysis investigating the incidence of dementia by birth year did not show any clear effect of birth cohort on incidence (Supplementary Figs. S1-4).

Fig. 2A and B show time trends in prevalence rates (presented as percent of the total elderly population) in women and men, respectively. Prevalence rates increased from 1996 to 2015 for both sexes in all age groups. The older the age group, the higher the prevalence. The prevalence rates were higher in women than in men aged 75 years and above. For both men and women, the prevalence rates have been relatively stable since 2010.

Fig. 3 and Supplementary Figs. S5 and S6 show overall trends in total incidence and prevalence. The total incidence increased from 4875 people diagnosed in 1996 to 8017 people in 2015. The highest incidence was observed in 2009 ( $n = 8832$ ). The prevalence increased from 14,019 people in 1996 to 36,129 people in 2015. The prevalence increased steadily over the total period, although with a lower rate of increase in most recent years.

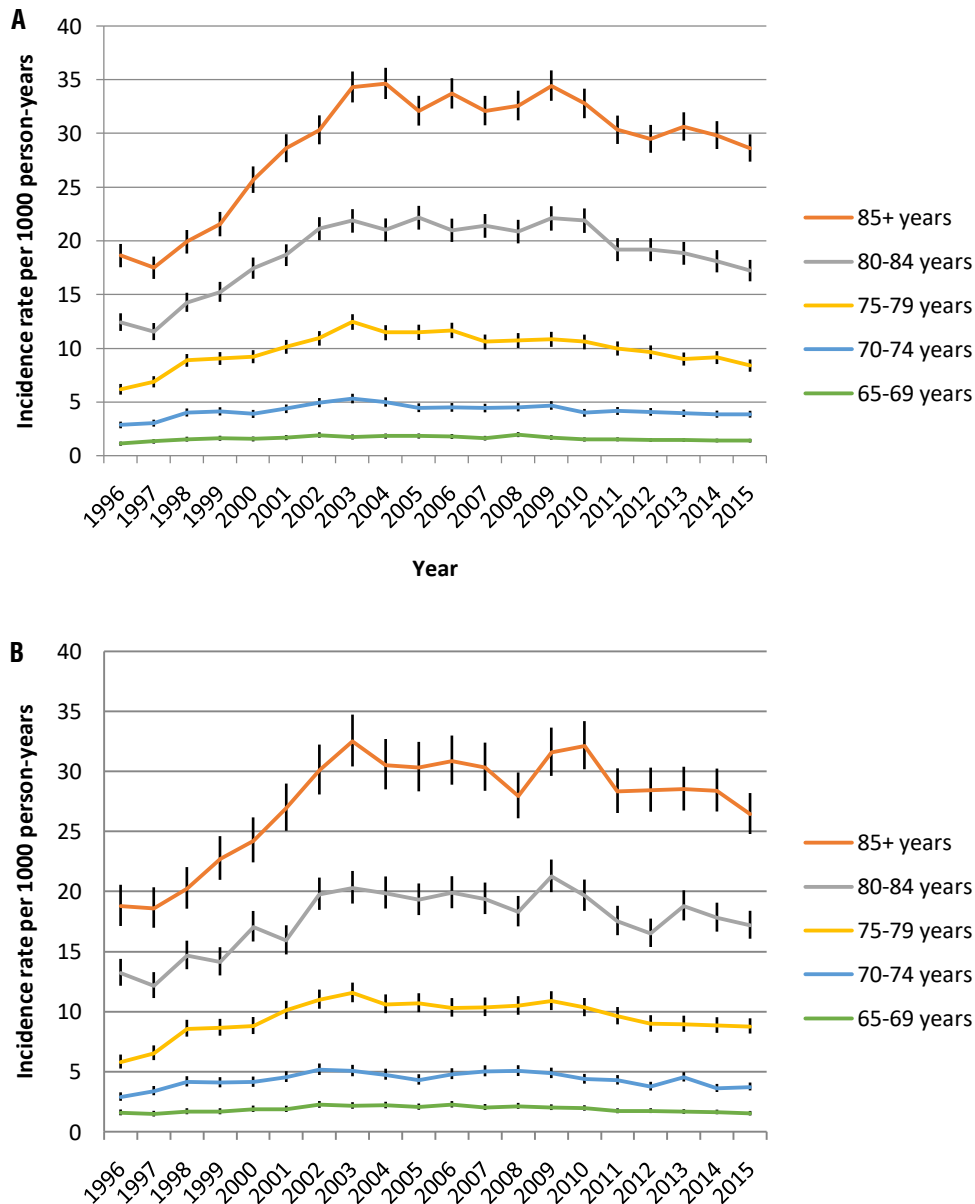


Fig. 1. (A) Time trend of incidence rates of dementia in Danish women from 1996 to 2015. Error bars represent 95% confidence intervals. (B) Time trends of incidence rates of dementia in Danish men from 1996 to 2015. Error bars represent 95% confidence intervals.

#### 4. Discussion

To our knowledge, this is the first complete national population study based on routine health care data to confirm trends in declining incidence of dementia that have previously been described in population-based research studies. For men and women in all age groups, incidence rates reached their peak values from 2003 to 2010, followed by a decline. Adjusted for age and sex, the incidence rate of dementia in the total population increased annually by 9%, on average, until 2003, followed by a 2% annual decline. The prevalence rates increased for men and women in all age groups during the whole period from 1996 to 2015, most predominantly in the oldest age groups. Thus, while incidence

rates stabilized around 2003 and have declined since 2010, the total prevalence of dementia is still increasing.

Several population-based studies have compared incidence and prevalence in two, or more, time intervals. Nine studies in high-income countries have investigated trends in dementia incidence using population-based cohort study designs: The Rotterdam Study: 1990 and 2000 (The Netherlands) [6]; The Cognitive Function and Aging Studies (CFAS): 1990-1994 and 2008-2011 (UK) [8]; The English Longitudinal Study of Aging: 2002-2013 (UK) [11]; The Indianapolis-Ibadan Dementia Project (IIDP): 1992 and 2001 (USA) [9]; The Framingham Heart Study: 1977-1983, 1986-1991, 1992-1998, and 2004-2008 (USA) [5];

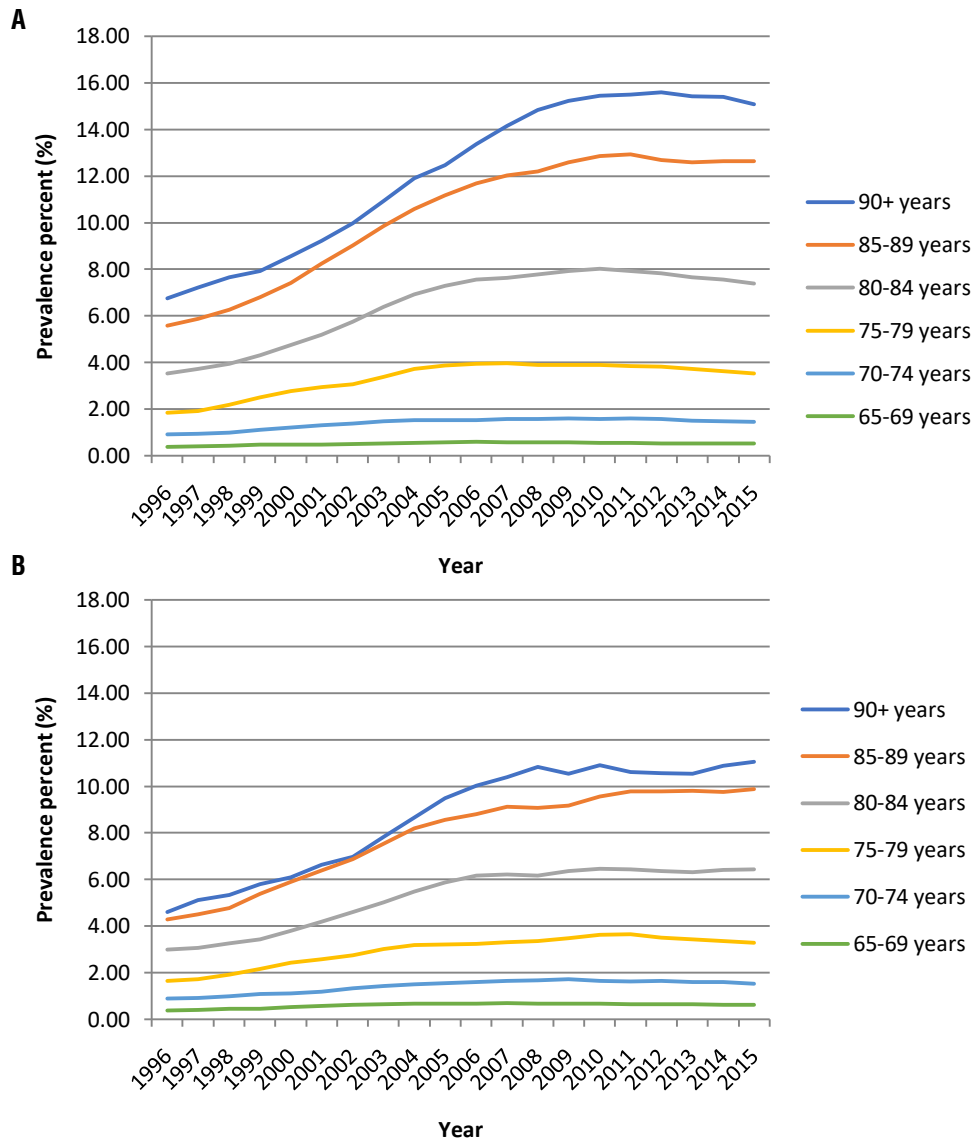


Fig. 2. (A) Time trends of dementia prevalence rates in Danish women from 1996 to 2015. (B) Time trends of dementia prevalence rates in Danish men from 1996 to 2015.

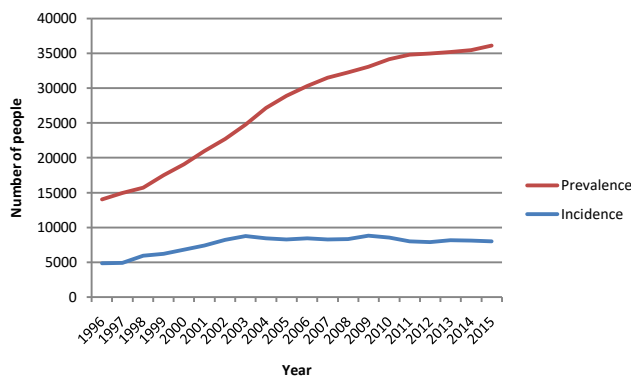


Fig. 3. Time trends of total incidence and prevalence of dementia in Denmark from 1996 to 2015.

The Chicago Health and Aging Project: 1994-1997, 1998-2000, 2001-2003, 2004-2006, 2007-2009, and 2010-2012 (USA) [17]; The Einstein Aging Study: 1993-2015 (USA) [10]; The Bordeaux Study: 1988-1989 and 1999-2000 (France) [7]; and The Hisayama Study: 1998 and 2012 (Japan) [18]. A recent meta-analysis included the Rotterdam Study, the IIDP, the Bordeaux Study, the CFAS, and the Hisayama Study [19]. Overall, the meta-analysis concluded that the results indicated a stabilizing trend in incidence of dementia rather than a decline [19]. It also found that the risk of bias for domains of external validity was high for all study populations, except for the UK and Japanese studies, indicating that the study populations could be unrepresentative of their national populations [19]. Furthermore,



they concluded that there was a risk of minimal nonresponse bias in the Rotterdam Study, the IIDP, the Bordeaux Study, and the Framingham Heart Study [19]. The quantitative synthesis suggested a nonsignificant decline of incidence of dementia; however, the heterogeneity between studies was high [19].

The declining incidence suggested in most of these studies may be related to changes over time in the risk factor profile. Thus, the Bordeaux Study found the later cohort was better educated, had a lower stroke prevalence, and used more antihypertensive and lipid-lowering drugs [7]. When adjusting for cardiovascular status and educational level, however, the association only explained some of the decrease seen in women [7]. The Framingham Heart Study found a decreasing effect of cardiovascular events and an increased effect of treatment with antihypertensive drugs on the risk of developing dementia in the later cohorts, although this benefit seemed to be more noticeable in people with at least a high school diploma [5]. When evaluating dementia subtypes, the Framingham Heart Study found a significant trend in decline only for vascular dementia, not AD, whereas the IIDP noted a decline in all-cause dementia and in AD [5,9]. The Hisayama Study reported a significant increase in incidence of AD, while incidence of vascular dementia remained stable over time [18]. This increase may partly reflect a difference in risk factor profiles and the ethnicity in high-income countries in the Western world and in East Asia.

Time trends in the incidence of dementia have also been reported in a few studies based on registry data. A German study evaluated incidence rates based on samples from health insurance data in 2006/07 and 2009/10 and reported a significant decline between the two time points [20]. Two Canadian studies assessed continuous time trends of incidence rates in the provinces of Saskatchewan (2005–2013) and Ontario (2002–2013), respectively, based on data from administrative health databases [21,22]. The Saskatchewan study reported a significant decline in incidence rates from 2005 to 2013 [21]. Findings from Ontario had a pattern similar to our study, with fluctuations from 2002 to 2008 followed by a decline, but the overall trend in declining incidence was only significant in women [22]. A Dutch registry-based study using data from primary care only reported an annual growth in incidence of 2.1% from 1992 to 2014 [23]. Registry-based data from hospitalized inpatients in Sweden on incidence rates of dementia from 1987 to 2016 demonstrated an increase until 2011, followed by a decline [24]. Thus, although there is a lack of consistency among results from registry-based studies, many have indicated stabilizing or declining trends in incidence rates of dementia during recent years, while some only observe these trends to be limited to subgroups and one study reported increasing incidence.

In our study, we also assessed time trends in prevalence rates. To sum up findings from ten population-based studies investigating time trends in the prevalence rates of dementia,

the IIDP, a Spanish study, and three Swedish studies observed a stable prevalence, whereas the CFAS and an American study found a declining prevalence and the Hisayama Study found an increasing prevalence [18,25–31]. The Chicago Health And Aging Project found substantial variation over time but no secular trend from 1994 to 2012 [17]. Using two different analytical approaches, the Bordeaux study described trends moving in opposite directions [32]. Most studies investigating prevalence of dementia reported trends in declining or stabilizing prevalence, while our study observed trends similar to the Hisayama Study, with increasing prevalence in both sexes and all ages during the 20 years.

Our study demonstrates the power of access to continuous data for assessing time trends as compared with using a few discrete time points. Had we only compared incidence rates in 1996 and 2015, the decline since 2009 would have been missed. Both the initial increase and later decline in dementia incidence rates should be interpreted in the context of increased public awareness of dementia. In Denmark, the first memory clinic was established in 1995 and the first pharmaceutical drug against AD was launched in 1997. These events have potentially contributed to an increase in public awareness, and we believe that the marked increase in incidence from 1996 to 2003 reflects an increased diagnostic rate, rather than an actual increase in incidence of dementia. Likewise, there is a possibility that the later decline could be partly related to a higher precision in diagnosis resulting in a more restrictive use of the diagnosis of dementia.

Thus, when interpreting possible causes for the stabilization and later decline in incidence, one hypothesis relates to improvement in health and another to improved precision in diagnosing dementia.

First, during the last decades, we have experienced a marked improvement in living conditions and health in Western high-income countries. We believe that the general improvement in health, including better control and treatment of risk factors, may prevent vascular cognitive impairment and may contribute to the observed decline in incidence of dementia in recent years.

In the Framingham Heart Study, the declining incidence was only significant for vascular dementia, and not AD [5]. The Hisayama Study reported stabilization in the incidence of vascular dementia whereas AD increased [18]. Results from magnetic resonance imaging scans performed in the Rotterdam Study showed that people in the 2000 cohort had lesser brain atrophy and fewer white matter lesions than those in the 1990 cohort [6]. Thus, the decline in incidence rates reported in Western high-income countries may mainly represent vascular dementia.

Our analysis of dementia incidence by birth year did not demonstrate any effect of birth cohort on incidence.

Second, even though the diagnostic criteria for dementia have not changed within our study period, there have been improvements over time regarding the application of neuroimaging and biomarkers for neurodegenerative

disorders. Consequently, the precision in diagnosis may have improved, especially when diagnosing subtypes of dementia. We cannot exclude the fact that this may have led to a more restrictive use of the dementia (syndrome) diagnosis during this period contributing to a change in diagnostic rate over time and an apparent decline in incidence.

Even though incidence rates are declining, our study shows that the number of people living with a registered dementia diagnosis in Denmark (prevalence) is still increasing. There are two possible explanations for this apparent paradox. First, the number of elderly people is increasing because of increasing life expectancy and large birth cohorts from the 1940s and 1950s having reached the elderly population. As the risk of dementia increases with age, we expect that the larger elderly population will lead to an increasing number of people living with dementia over the next decades. The large birth cohorts from the 1940s also explain the fact that the median age of our total elderly population declined from 74.2 years to 72.9 years from 1996 to 2015 [33]. Second, people may live for a longer time registered with dementia because of either earlier diagnosis or decline in mortality. If our study population was registered with dementia at an earlier age later in our study period, this may have led to an increased amount of time lived with a diagnosis. However, the median age of incidence of dementia was 82.4 years in 1996 and 82.3 years in 2015. Hence, we do not believe this explanation to be very likely. As life expectancy is increasing in the general population, there is a possibility that individuals diagnosed with dementia live for a longer time with their diagnosis than previously. Population-based studies from Stockholm, Rotterdam, and Hisayama have reported declining mortality over time in people with dementia [6,18,29]. Thus, we believe it to be possible that individuals with dementia live longer after being diagnosed, which contributes to the continued increase in prevalence.

#### 4.1. Limitations of the study

This study was based on registered diagnoses from secondary health care and prescription data identifying 36,129 people living with dementia aged 65 years or more in 2015. Based on extrapolation from European population-based studies, it is estimated that approximately 87,000 people in Denmark aged 60 years or more are living with dementia, likely leaving a large proportion of undiagnosed cases of dementia [34]. Thus, as in many other countries, the diagnostic rate may be relatively low. Our study is based on national health care data from the secondary health sector and the Danish National Prescription Registry. Thus, our data reflect diagnoses established in routine medical care and do not include information on clinical manifestations, the level of cognitive decline, or diagnostic workup leading to the diagnosis.

National clinical and evidence-based guidelines have been available in Denmark since 1998, and ICD-10 criteria were applied for the (syndrome) diagnosis of dementia throughout the entire period. Brief cognitive testing was recommended to support a diagnosis of dementia in all recommendations. Our registry-based data do not inform us to which extent these recommendations were followed when physicians were making the diagnosis. However, in a previous study, we evaluated the quality of the registered cases of dementia in the Danish health care registries and found that the diagnoses of dementia were justified in 85.8% of the cases in elderly people [35]. Unfortunately, as a large proportion of the patients were registered with a diagnosis of “unspecific dementia,” our registry-based data are not sufficient for clarifying the etiology of dementia.

#### 4.1.1. Strengths of the study

Government-funded, universal health care, combined with unique personal identification numbers, provides an excellent setting for epidemiological studies. Our study was based on data using an entire population as the cohort, which means it is large, has no dropouts, and represents trends in an entire nation. Data in the Danish registries are continuously updated and data on follow-up are, for all practical purposes, complete and registered continuously in all calendar years.

This study assessed national trends in incidence and prevalence in Denmark, and we assume that these trends can be generalizable to other Western high-income countries that have similar access to diagnostic evaluation and support.

## 5. Conclusions

In conclusion, our study shows that incidence rates of dementia have declined since 2010. The total incidence of dementia has also declined, while the total prevalence is still increasing, albeit less rapidly in recent years. When planning future health care services, it is crucial to take the increasing number of people living with a dementia diagnosis into account. In future models for estimating projections of prevalence and incidence, the fluctuations in incidence rates and prevalence percentage over time should be considered. The decline in total incidence and incidence rates of dementia leads to a cautious optimism that with better health and management of risk factors, it may be possible to lower the risk of dementia. However, previous studies imply that this effect may be limited to vascular dementia, highlighting the need for better prevention and treatment of AD and other neurodegenerative dementias.

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this report. The corresponding author has had full access to all the data used in this study and takes full responsibility for the decision to submit for publication.

Authors' contribution: A.N., G.W., and L.T. contributed to the study concept and the literature review. A.N., G.W., T.M.L., and L.T. designed the study. The statistical analyses were carried out by T.M.L., and L.T. G.W., and L.T. did the outline for the manuscript and L.T. wrote it. All authors contributed to interpreting the data and to the critical review of manuscript content.

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### Supplementary data

Supplementary data related to this article can be found at <https://doi.org/10.1016/j.jalz.2019.07.006>.

### RESEARCH IN CONTEXT

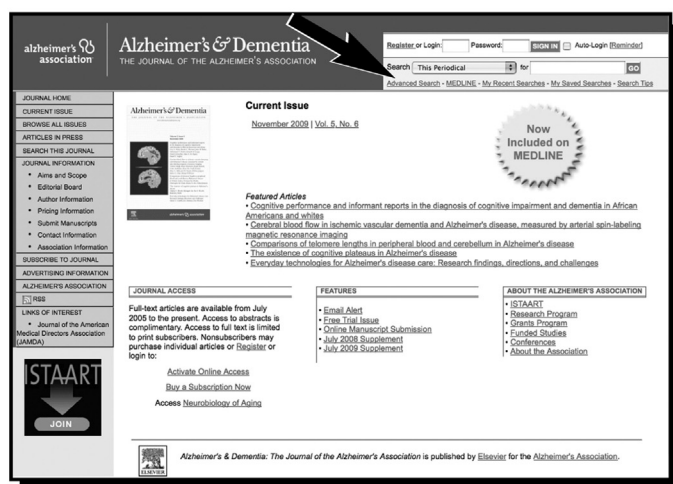
1. Systematic review: The authors reviewed the literature using a PubMed search. Even though there was evidence of declining or stabilizing incidence of dementia in Western high-income countries, the number of studies was small and the heterogeneity of findings was high.
2. Interpretation: Studying an entire national population based on high quality routine health care data from the secondary sector, we observed that the age- and sex-adjusted incidence rate increased, on average by 9% annually from 1996 to 2003, followed by a 2% annual decline from 2004 to 2015. While the total incidence and incidence rates declined, the total prevalence was still increasing.
3. Future directions: Future healthcare planning on prevention and management of dementia should take these findings into account. More studies are needed to clarify whether the decline in incidence of dementia is limited to vascular dementia. This would emphasize the great need for targeted treatment for neurodegenerative dementias.

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